IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Mouritsen et al.
Serial No.	:	08/955,373
Filed	:	October 21, 1997
Examiner	:	Ron Schwadron
Art Unit	:	1644
For	:	**INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES**

745 Fifth Avenue, New York, New York 10151

DECLARATION OF JAKOB SCHMIDT, M.Sc.

Commissioner for Patents
Washington, D.C. 20231
Dear Sir:

JAKOB SCHMIDT declares and says that:

1. I am the Chief Financial Officer of Pharmexa A/S (Pharmexa), and have held this position since about February 2000. Prior to being the CFO of Pharmexa, I was a Project Manager with Carnegie Bank Corporate Finance for 6 years, responsible for Carnegie's Healthcare and Equity Capital Market activities in Denmark. I have managed a number of initial public offerings (IPOs) and private placements in biotechnology companies and other high growth companies in recent years. Prior to joining Carnegie, I undertook Ph.D. studies at the Institute of Finance, Copenhagen Business School, focusing on the financial problems of start up, high growth companies and teaching a number of graduate and undergraduate courses on high technology and start-up financing at Copenhagen Business School. I have also studied medicine at Aarhus University and international economics and finance at Brandeis University, Boston. I am also a member of the Board of Directors of Inoxell A/S, and of the Danish Investor Relation Society (DIRF). I am responsible for Pharmexa's financial activities, and am authorized to speak on behalf of Pharmexa. Pharmexa is the assignee of the above-captioned application (the present application), by virtue of assignment from the inventors and a corporate name change (from M&E Biotech). From my education, training and experience, including my experience, including my experience at Pharmexa, I am familiar with the subject matter of the present application, including that I am informed that a concurrently-filed Amendment presents claims as reproduced below or substantially as reproduced below, after my signature, which I

have read and understood. Accordingly, I respectfully submit that I am well qualified to speak as to the present application, and particularly, success of the present invention, such as the commercial or financial success of the present invention, including financing generated. I am advised that success, such as commercial success, of an invention is an indicia of patentability; and, I respectfully request that the success, including the commercial or financial success of the present invention be fully considered as demonstrating the patentability of the present invention. At Pharmexa, we proudly refer to the present invention as AutoVac™ technology; and, this term shall also be used herein.

A BRIEF HISTORY OF PHARMEXA
– EARLY AND CONTINUOUS
COMMERCIAL OR FINANCIAL
SUCCESS BY THE PRESENT INVENTION

Some Commercial Or Financial Successes

2. a. In **1992**, Pharmexa entered into a **collaborative agreement with Ferring Pharmaceuticals A/S,** spurred by Pharmexa's discovery of the AutoVac™ technology. Also in 1992, the first general proof of principle for the AutoVac™ technology was obtained and the priority application of the present application was filed in 1993.

b. **Pharmexa's first private placement of shares** was successfully completed in May **1997**, contributing **net proceeds to the Company of DKK 75 million**. **Subsequent** thereto Pharmexa obtained **loan financing** from Business Development Finance **totaling DKK 21 million**. Also, in **1997**, Pharmexa entered into a **license agreement** providing **Ferring** the global rights to all human therapeutic indications of the AutoVac™ TNF-alpha pharmaccine. **Ferring pays certain costs** involved with the program which is a subject of the license, and Pharmexa acts as consultants for Ferring during the pre-clinical and clinical development and in the event of future sublicensing.

c. **A second private placement** took place in June **1999**, **providing net proceeds to Pharmexa of DKK 31** million.

d. In March **2000**, Pharmexa entered into a **collaboration with Schering-Plough Animal Health (SPAH)** regarding pharmaccines for **veterinary use** based on **Pharmexa's AutoVac™ technology**. On a global, exclusive basis **Schering-Plough received** a **license** for use of the AutoVac™ technology **in the veterinary field. Schering-Plough pays all research, development, manufacturing and marketing costs. Schering-Plough has paid to**

Pharmexa a technology transfer fee and will pay up-front and milestone payments on each product. **Pharmexa will eventually also receive a royalty of Schering-Plough's net profit from product sales.**

e. In April **2000, Pharmexa and Ferring announced the approval of the first clinical trial on cancer patients** with the present invention - AutoVac™ technology - wherein the self-protein is human TNF-alpha **and** later that month **Pharmexa entered into a research and development collaboration with H. Lundbeck** regarding the use of the present invention - AutoVac™ technology as to neurodegenerative diseases. Pursuant to the agreement, **H. Lundbeck pays all expenses related to the program** which is the subject of the license, and **H. Lundbeck paid a down-payment to Pharmexa**. Furthermore, depending on results obtained, **H. Lundbeck can pay Pharmexa as to its license** pertaining to the present invention, **total milestone payments of approximately DKK 150 million** over the entire duration of the project. **Pharmexa will also receive royalties on the sale of final products.** And, **H. Lundbeck also invested DKK 10 million in connection with Pharmexa's IPO on the Copenhagen Stock Exchange** (*see infra*).

f. Late **May 2000, Pharmexa was listed on the Copenhagen Stock Exchange, providing DKK 375 million in net proceeds i.e. as previously alluded to, there was an Initial Public Offering (IPO); it raised more than DKK 375 million in net proceeds.**

g. In December **2001 Pharmexa announced** an AutoVac™ **cancer license option to Lexigen Pharmaceuticals, Corp**., a **subsidiary of Merck KGaA** of Darmstadt, Germany, located in Lexington, Massachusetts.

h. In April **2002 Pharmexa announced** that **GlaxoSmithKline has an exclusive option on a HER-2 Protein Breast Cancer project**.

The Commercial And Financial Successes Are Due to The Instant Invention And Technical And Patent Professionals Must Have Favorably Considered the Present Invention

3. a. Thus, as to the present invention Pharmexa has collaborative partners includeing: Ferring; H. Lundbeck; Schering-Plough; and Lexigen/Merck KgaA. Pharmexa has raised capital as detailed herein (e.g., private placements, loan, IPO). From my education, training and experience, it is not uncommon, prior to a typical agreement of the nature of those herein mentioned, it is not uncommon for there to have been an analysis of the present invention

by technical and patent professionals ("due diligence"). Furthermore, from my education, training and experience, it is typical for capitalization of the nature discussed herein, for there to have been an analysis by technical and patent professionals ("due diligence") as to technology of Pharmexa, including the present invention, and especially the present invention, considering that the present invention is a basic, core technology of Pharmexa. Thus, based on my education, training and experience, the agreements Pharmexa has entered into with its partners, as well as the capitalization, have been based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrate commercial and financial success of the present invention. Indeed, note both direct and indirect revenue herein discussed.

b. As yet a further indicia of patentability, it is noted that while the USPTO is not bound by decisions of foreign patent offices, nonetheless, foreign patents corresponding to the present application have been granted, over art as cited against the present application, showing that others skilled in the art and in the patent field have recognized the patentability of the present invention (e.g., Examiners in foreign patent offices). And, on this point, it is noted that in accordance with the foregoing mention of "due diligence", the many entities that have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, demonstrate that others skilled in the art and in the patent field have recognized the patentability of the present invention. Simply, the many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, as well as the grant of foreign patents, demonstrates that technical and patent professionals must have favorably evaluated the present invention and particularly its position in the art and its patentability.

c. In my opinion, based on my education, training and experience, including my experience prior to joining Pharmexa and at Pharmexa, key to investment decisions made by third parties as to Pharmexa, and to decisions to enter into agreements with Pharmexa as to the present invention, as herein detailed, are the important medical, veterinary and commercial implications of methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in claims understood to be added or substantially added, which was recognized by Mouritsen et al in the present application.

d. Furthermore, as to the aforementioned due diligence, in my opinion, based on my education, training and experience, including my experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that the due diligence included analysis of the present application, the prior art now cited in the prosecution thereof, the scientific literature, expert opinions and currently available therapies. Based on these analyses, I respectfully submit that Pharmexa's partners and investors. recognized the potential to develop new treatments for diseases by employing methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in claims understood to be added or substantially added, and as described in the present application.

e. More specifically, as to the aforementioned due diligence, in my opinion, based on my education, training and experience, including my experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that the due diligence included analysis of Russell-Jones, WO 92/05192 and Hellman WO 93/05810 or equivalent documents, and agreements have been entered into with Pharmexa and money was and continues to be invested in Pharmexa, because the inventions described in the present application were and are recognized to be novel and non-obvious in the face of the said prior art, and to meet unmet medical and veterinary needs. In my opinion, based on my education, training and experience, including my experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that although many factors influence decisions taken to enter into agreements and make investments as herein detailed, the decision to enter into agreements and invest as described herein was made with significant consideration for the market potential for the technology of the present application and the importance of the present application in establishing a market potential and thus value for the technology. Also, in my opinion, based on my education, training and experience, including my experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that the present invention, including methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in claims understood to be added or substantially added, and as described in the present application, is highly valuable, is highly relevant to today's healthcare (medical and veterinary) needs, and thus

is highly attractive for investment and funding and licensing and collaboration; and, was not previously taught or suggested.

CLEAR AND CONVINCING EVIDENCE OF COMMERCIAL AND FINANCIAL SUCCESS, AND PATENTABILITY, OF THE INSTANT INVENTION HAS BEEN PROVIDED

4. I respectfully submit that the foregoing provides, *inter alia*, clear and convincing evidence of the commercial and financial success and patentability of the present invention: Clearly, many entities have entered into agreements concerning the instant invention; many have invested in the instant invention; and foreign patent offices have recognized the patentability of the instant invention; *inter alia*. Indeed, it is also noted that many are employed as a result of the instant invention - directly by Pharmexa and indirectly by collaborators who work with respect to embodiments of the instant invention – and, that this further demonstrates investment and proceeds spent as to the present invention, and that this thereby further demonstrates commercial and financial success of the instant invention. Hence, I respectfully submit that I have provided, *inter alia*, clear and convincing evidence of the commercial and financial success and patentability of the present invention.

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 14.5.2002 By: Jakob Schmidt
JAKOB SCHMIDT, M.Sc.

CLAIMS UNDERSTOOD TO BE ADDED OR SUBSTANTIALLY ADDED

--56. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

57. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

58. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

59. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

60. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

61. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

62. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

63. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving

secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

64. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

65. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

66. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

67. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

68. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

69. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

70. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier

protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

71. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

72. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier

protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein

with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

73. (New) The method of any one of claims 56-72 wherein the modified self-protein is a recombinant modified self-protein.

74. (New) The method of any one of claims 56-72 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

75. (New) The method of claim 73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

76. (New) The method of any one of claims 56-72 wherein the administering includes administering an adjuvant.

77. (New) The method of claim 76 wherein the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer.

78. (New) The method of claim 73 wherein the administering includes an adjuvant.

79. (New) The method of claim 75 wherein the administering includes an adjuvant.--